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| 09/257,650 | 02/25/1999 | MASAHIKO FUJINO | 48194 | 2632 |

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| EXAMINER |
|---|
| O HARA, EILEEN B |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/257,650 | FUJINO, MASAHIKO | |
| | Examiner | Art Unit | |
| | Eileen B. O'Hara | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14,16-19,21-24 and 26-44* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16-19,21-24 and 26-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14,16-19,21-24 and 26-44* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Continued Prosecution Application*

1. The request filed on June 26, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/257,650 is acceptable and a CPA has been established. An action on the CPA follows.

### *Status of Claims*

2. Claims 1-14, 16-19, 21-24 and 26-44 are pending in the instant application. Claims 14, 16, 17, 21, 2427 have been amended, claims ## have been canceled and claims 39-44 have been added as requested by Applicant in Paper Number 23, filed June 26, 2002.

Claims 1-13 are withdrawn as being drawn to a non-elected invention.

Claims 14, 16-19, 21-24 and 26-44 are currently under examination.

### *Claim Objections*

3. Claim 44 is objected to because of the following informalities:

3.1 On the sixth line of the claim, after the word "providing", there is the word "the" that has been struck through and should be deleted.

3.2 In claims 27 and 44, second line of section 5, the word "does" should be inserted between the words " and" and "not" to be grammatically correct.

Appropriate correction is required.

### *Withdrawn Rejections*

4. The rejections of claims under 112 § 2 are withdrawn in view of Applicants' amendment.

***Rejections Over Prior Art***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5.1 Claims 14, 16-19, 24, 26-38 remain rejected under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al., Molecular Endocrinology 8(7):886-894, 1994, for reasons of record in Paper No. 18, pages 2-3, and Paper No. 20, pages 3-4.

Applicant has amended the claims to recite a new limitation in which a comparison is made between activation of a non-aberrant receptor by a ligand which operates the non-aberrant receptor but does not operate the aberrant receptor, and the activation of an aberrant receptor with a substance to be screened, wherein a similar activity indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

The teachings of Birnbaumer et al. were discussed in the previous Office Actions, Paper No. 18, pages 2-3, and Paper No. 20, pages 3-4.

Applicant traverses the rejection, and disagrees with the Examiner's interpretation of Birnbaumer. Applicant asserts that while AVP causes the mutant receptor to have adenylyl cyclase activity, like the wild-type receptor, the potency of AVP is significantly low, in that it causes a disease, congenital nephrogenic diabetes insipidus (CNDI), and thus the reference fails

to teach or suggest the testing or screening of compounds that cause the mutant receptor to operate in a manner similar to the wild-type receptor as presently claimed.

Applicant's arguments have been considered but are not persuasive. While Birnbaumer et al. did not find a compound that caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, as presently claimed, that is not the relevant issue. It is the method steps that are anticipated, and the result obtained in the prior art using those method steps are not relevant. Birnbaumer et al. meets the limitations of all the steps, that of bringing the aberrant receptor into contact with a subject substance (Q3 receptor and AVP and dDAVP), determining the activity of the receptor with the compounds, bringing the non-aberrant receptor into contact with a subject substance (wild-type receptor and AVP and dDAVP), determining the activity of the receptor, and comparing the activities of the two receptors with the compounds. The assay method of Birnbaumer et al. *would* be able to find a compound that caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, if other compounds were screened. As evidence of this, while one of the compounds screened (dDAVP) did not activate the human mutant receptor in a manner similar to that of the wild-type receptor, it did activate a mutant type-2 vasopressin receptor in dogs. Birnbaumer et al. teach that a strain of dogs with CNDI has a receptor with a 10-fold reduced affinity for AVP, and in dogs, the symptoms of the disease could be relieved by frequent administration of deamino[8-D-Arg]vasopressin (dAVP), which is a V2R-selective agonist (see pages 890-892). Birnbaumer et al. tested both AVP and dDAVP for activity on the mutant and wild-type V2 receptors, and found that the $EC_{50}$ for adenlyl cyclase activation was essentially the same for AVP and dDAVP. Similar changes to those observed for AVP in the affinity and

adenylyl cyclase activation by the dog mutant receptor were observed for dDAVP (that is, reduced binding and activation), but frequent administration of dDAVP in dogs relieved the symptoms of the disease. Human CNDI patients having the Q3 mutation were also administered very high doses of dDAVP (page 891), in which levels of dDAVP were almost 1000-fold higher than the concentration of AVP measured in the blood of normal subjects, yet there was no physiological response obtained. The difference between the response seen with the dogs and the human subjects was ascertained to be due to the fact the density of the mutant receptor in the dogs was the same as the density of wild-type receptor in normal dogs, while the receptor density in human patients having the Q3 receptor mutation is significantly reduced compared to receptor density in normal subjects, and that the combination of low affinity for AVP and reduced receptor number probably accounts for the unresponsiveness of the Q3 patients to dDAVP.

For these reasons and those of record in the previous Office Actions, Birnbaum et al. anticipates the claims and the rejection is maintained.

5.2 Claim 14 remains rejected under 35 U.S.C. 102(b) as being anticipated by Green et al., J. Biol. Chem. 268(31):23116-23121, 11/5/93, for reasons of record in Paper No. 18, page 3, and Paper No. 20, pages 4-5.

Applicant traverses the rejection and asserts that this reference fails to anticipate claim 14, because Green et al. fails to teach that dopamine, although it had similar binding affinity to both the mutant and wild-type receptor, did not cause the operational activity of the mutant AR receptors to function in a manner similar to that of the wild-type receptor, and so fails to teach every element or the claim.

Applicants arguments have been considered but are not persuasive. Though Green et al. do not specifically state that they were screening for compounds that restore wild-type activity to the receptor, they were screening for compounds to determine the effect of the compound on activity of the receptor, and found that dopamine (see abstract and Table 1) had the same effect on both the wild-type and mutant receptor. Green et al.'s intent is not at issue nor is the result of the screening process, that is, not finding a compound that would restore wild-type activity to a mutant receptor; his method anticipates the currently claimed methods as it has all recited method steps and would detect compounds that restore activity. Therefore, Green et al. anticipates the claim and the rejection is maintained.

5.3 Claim 14 remains rejected under 35 U.S.C. 102(b) as being anticipated by Kong et al., J. Biol. Chem. 268(31):23055-23058, 1993, for reasons of record in Paper No. 18, page 3, and Paper No. 20, pages 5 and 6.

Applicant traverses the rejection and submits that Kong merely studies the binding affinity of certain agonists to the mutant and wild type receptors, but fails to teach the change in operation activity of the mutated receptor to function like the wild type receptor.

Applicant's arguments have been considered but are not persuasive. Kong et al. teach more than binding assays. See page 23056 and Figure 2, in which COS-7 cells were transfected with either the wild type or D95N mutant, stimulated with forskolin in the presence or absence of opoid agonists, and cAMP formation was measured. As discussed above, the result of the screening process is not the issue; his method anticipates the currently claimed methods as it has all recited method steps and would detect compounds that restore activity. Therefore, Kong et al. anticipates the claim and the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6.1 Claims 14, 16-19, 21-24 and 26-38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., J. Biol Chem. 268(15):11272-11277, 5/25/93, in view of Choong et al., J. Clin. Endocrinol. Metab. 81(1):236-243, 1996, both previously of record, for reasons cited in the previous Office Actions, Paper No. 18, at pages 4-5, and Paper No. 20, at pages 6-7, and below.

Applicant submits that the Examiner has picked and chosen teachings from the two references to combine the methods of the present invention, and that this is simply improper. Applicant asserts that the Examiner has simply failed to show that one of ordinary skill in the art would have been motivated to combine the references, and that the two references each address a different disease and a different receptor, and that there would be no reason for one of ordinary skill in the art that was interested in studying an androgen insensitivity to look to an article addressing an insulin receptor mutation. Applicant also asserts that the Examiner is using impermissible hindsight by arguing that the motivation is provided by the combination of the references, and that this is an improper analysis under § 103, and that the Examiner is using impermissible hindsight to select teachings from the references to fit the rejection. Applicant also assert that as set forth in Applicant's previous response, the methods of the present invention do not use, or seek to screen for, antibodies that compensate for the mutation.

Applicant's arguments have been considered but are not persuasive. The claims do not include the limitation that the substance to be screened may not an antibody. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, although the references address different types of receptors and diseases, they are both receptors, and one of ordinary skill in the art of receptor function would be interested in looking at research at other types of receptors, because even different receptors have common general functions, and studies on one type can yield information relevant for anther type of receptor.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

For these reasons and those of record in the previous Office Actions, the rejection is maintained.

6.2 Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al., and further in view of Dower et al., U.S. Patent No. 5,639,603, June 17, 1997.

New claims 39-44 encompass the inventions claimed in claims 14, 16, 17, 21 and 24, respectively, with the additional limitation that the compound that is screened for the ability to activate an aberrant receptor is a synthetic compound.

The teachings of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. and Choong et al. were discussed above and in the previous Office Actions, Paper Nos. 18 and 20. These references do not disclose screening synthetic compounds.

Dower et al. teaches that large collections of synthetic compounds can be generated and screened to identify and isolate compounds with useful properties (see entire patent), that peptide or other molecular libraries can be generated using unnatural amino acids and other molecular building blocks, so that accessible sequence and structural diversity is dramatically increased (see column 1, lines 46-55, for example), and that high throughput screening of collections of chemically synthesized molecules and of natural products has traditionally played a central role in the search for lead compounds for the development of new pharmaceutical agents (see column 2, lines 38-60).

At column 11, lines 6-13, Dower et al. states:

> The library is screened to identify "active recipes" that then can be reproduced on a preparative scale and fractionated (if necessary) to isolate the bioactive component(s). The encoded library technologies have considerable potential to expand the scope of combinatorial chemistry and its applications to drug discovery and the development and isolation of a wide variety of useful compounds.

Dower et al. specifically teaches that such libraries of synthetic compounds can be incubated with receptors to determine if binding to the receptors has occurred (see claim 1, and column 16, lines 48-54, and column 31, line 10 to column 37, line 42, for example).

At column 31, lines 16-23, Dower et al. states:

> By way of example, such libraries can be used in assays to identify ligands that bind receptors, such as peptides and nucleic acids that bind to proteins, drugs that bind therapeutic target receptors, and epitopes (both natural and synthetic) recognized by antibodies, as well as to identify a variety of compounds with pharmaceutical, agricultural, and medical diagnostic applications.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made use the screening methods of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al. to screen large libraries of synthetic compounds made by combinatorial chemistry, as taught by Dower et al. The skilled artisan would be motivated to do so in order to rapidly screen large numbers of compounds that could bind to and activate an aberrant receptor in order to discover new compounds with desired pharmacological properties, as taught by Dower et al. There would be a reasonable expectation of success, since the generation and screening of combinatorial libraries has been widely and successfully used in the field of drug discovery.

***Conclusion***

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

LORRAINE SPECTOR
PRIMARY EXAMINER